REMARKS

Claims 1 to 17 are pending. Claims 1 to 7 have been cancelled, and new claims 23 to 27 added herein. Thus, upon entry of the present amendments, claims 8 to 17 and 23 to 27 will be under examination.

Regarding the New Claims

New claims 23 to 27 are supported by the specification and claims as originally filed and do not add new matter. In particular, new claim 23 is directed to a method of selectively inducing apoptosis in normal prostate tissue *in vivo* by administering to a subject a chimeric prostate-homing pro-apoptotic peptide that contains a prostate-homing peptide linked to an antimicrobial peptide, where the chimeric peptide exhibits selective toxicity to normal prostate tissue and where the antimicrobial peptide has low mammalian cell toxicity when not linked to the prostate-homing peptide. Support for new claims 23 to 27 is found in original claim 1 and in the specification, for example, at page 8, lines 16-23, which discloses induction of apoptosis by SMSIARL-$GG_D(KLAKLAK)_2$ in the normal mouse prostate. Support for new claims 23 to 27 also is found in the specification, for example, at page 74, lines 8-18, and page 106, lines 2-14, which discloses selective induction of apoptosis in prostate tissues by chimeric peptide SMSIARL-$GG_D(KLAKLAK)_2$ following systemic administration, with no evidence of apoptosis in non-prostate tissues. Thus, the new claims are supported by the specification and claims as

originally filed and do not add new matter. Applicants therefore respectfully request that the Examiner enter the new claims.

Regarding the Drawings

Filed concurrently herewith is a separate paper with the proposed drawing corrections and new drawings. In the separate paper, the changes to the drawings are indicated in red ink in accordance with 37 C.F.R. § 1.85. Applicants respectfully request that the separate paper be considered, the new drawings entered, and that the objection to the specification regarding the drawings be removed.

Regarding the § 103 rejection of claims 8 and 13

The rejection of claims 8 and 13 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. is respectfully traversed.

The Office Action asserts that it would have been obvious to attach antimicrobial peptides known in the art to known prostate-homing peptides and also obvious to selectively direct the chimera to prostate with a reasonable expectation of success in killing prostate cancer cells ***without causing generalized side effects*** (Office Action at page 5, lines 2-4). Similarly, it is alleged that one skilled in the art would have been motivated to use a prostate targeting peptide attached to a

cytotoxic moiety in order to selectively produce apoptosis in prostate cancer ***without damaging other tissues, thereby minimizing unnecessary side effects*** (Office Action at page 5, lines 24-26).

Applicants contend that, prior to the invention, there was no teaching or suggestion of an antimicrobial peptide as part of a chimeric peptide with a prostate-homing peptide. At best, antimicrobial peptides had been used alone as anti-bacterial agents or suggested to be useful alone in lysing cancer cells. However, the cited art, neither alone nor in combination, teaches or suggests combining an antimicrobial peptide with a prostate-homing peptide to produce a chimeric peptide as recited in the claimed methods.

Specifically, Arap et al. describe tumor treatment with drug conjugates such as doxorubicin conjugates but do not teach or suggest a chimeric peptide that includes an antimicrobial peptide. The secondary reference by Fossa et al. reports the need for prostate cancer treatments that minimize generalized toxic effects but, again, does not teach or suggest a chimeric peptide which includes an antimicrobial peptide. Additional secondary references (WO 90/12866, U.S. Patent No. 5,789,542, and Javadpour et al.) report the anti-bacterial properties of antimicrobial peptides, alone, and the low mammalian cell toxicity of such peptides, but do not teach or suggest a chimeric peptide which includes such an antimicrobial peptide linked to a prostate-homing peptide. Furthermore, Bessalle et al. and Alvarez-Bravo et al. describe all-D-enantiomers of antimicrobial

peptides yet, like the references described above, do not teach or suggest a chimeric peptide containing an antimicrobial peptide in combination with a prostate-homing peptide. In sum, irregardless of any description of the use of antimicrobial peptides alone, the cited references, neither alone nor in combination, teach or suggest the use of an antimicrobial peptide as a component of a chimeric peptide together with a prostate-homing peptide.

Furthermore, prior to the present invention, there was no motivation for one skilled in the art to substitute a chimeric peptide for the use of an antimicrobial peptide alone. Specifically, one of ordinary skill in the art would not, as asserted by the Examiner, have been motivated to avoid "generalized side effects" since one would not have expected such "generalized side effects" with antimicrobial peptides alone. Generalized side effects such as the side effects observed with systemic anti-cancer therapy are due to non-selective effects of cytotoxic drugs on ***normal*** cells. As is well known in the art, a side effect such as nausea occurs due to the effect of cytotoxic drugs on ***normal*** proliferating cells of the gut, a side effect such as hair loss occurs due to the effect of cytotoxic drugs on ***normal*** proliferating cells in hair follicles, and a side effect such as immune suppression occurs due to the effect of cytotoxic drugs on ***normal*** proliferating immune cells. In the present case, the art does not teach or suggest to the skilled person that there are generalized side effects on normal cells when antimicrobial peptides are used alone. As an example, U.S. Patent No. 5,789,542 reports amphipathic lytic peptides with

anti-bacterial properties at concentrations that are not lethal to "normal mammalian cells" (abstract). Similarly, WO 90/12866 reports that neoplastic cells are lysed by lytic peptides while normal cells are not lysed (page 21, lines 19-27). In the absence of lytic activity against ***normal*** cells, one skilled in the art would not have expected generalized side effects due to the use of antimicrobial peptides alone, and, therefore, would have had no motivation to prepare a chimeric peptide containing an antimicrobial peptide in combination with a prostate-homing peptide in order to avoid such side effects. Because none of the cited references, alone or in combination, teach or suggest ***generalized side effects*** against normal mammalian cells ***when antimicrobial peptides are used alone***, there would have been no motivation to make the claimed invention.

In view of the above remarks, Applicants submit that claims 8 and 13 are unobvious over the cited references and respectfully request that the Examiner remove the rejection of these claims under 35 U.S.C. § 103.

Regarding the § 103 rejection of claims 9 and 14

The rejection of claims 9 and 14 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. as applied to claims 8 and 13 and further in view of

WO 99/46284, is respectfully traversed. WO 99/46284 is cited as allegedly describing the prostate-homing sequence of SEQ ID NO: 207 recited in claims 9 and 14.

For the same reasons discussed above in regard to claims 8 and 13, claims 9 and 14, which depend on claims 8 and 13, are unobvious over the cited references. At best, the additional reference, WO 99/46284, reports specific prostate-homing peptides but does not teach or suggest the use of a chimeric peptide in which an antimicrobial peptide is linked to a prostate-homing peptide. In the absence of any credible motivation to combine the cited references as discussed above, Applicants submit that claims 9 and 14 are unobvious over the cited references. Applicants therefore respectfully request that the Examiner remove the rejection of claims 9 and 14 under 35 U.S.C. § 103.

Regarding the § 103 rejection of claims 10 and 15

The rejection of claims 10 and 15 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. as applied to claims 8 and 13 above, and further in view of Ellerby et al., is respectfully traversed. Ellerby et al. is cited as allegedly describing the all-D enantiomer, $_{D}(KLAKLAK)_{2}$ (SEQ ID NO: 200), recited in claims 10 and 15, and Bessalle et al. and Alvarez-Bravo et al. are cited as describing possible advantages of all-D-enantiomers.

As discussed above, none of the references cited in the Office Action in regard to claims 8 and 13, alone or in combination, teach or suggest chimeric peptides which include an antimicrobial peptide linked to a prostate-homing peptide. Furthermore, the cited reference by Ellerby et al. is not prior art with respect to the claimed invention because Applicants reduced the invention to practice prior to September of 1999, when Ellerby et al. was published. As evidence that publication of the Ellerby et al. reference was not before Applicants' date of invention, Applicants submit herewith a Declaration under 37 C.F.R. § 1.131 along with copies of relevant documentary evidence. The dates on the documentary evidence have been redacted; however, the dates shown in the original documents indicate that Applicants had obtained the a chimeric peptide containing a prostate-homing peptide linked to an antimicrobial peptide and demonstrated selective cell death in prostate tissue prior to September of 1999. Because the Ellerby et al. reference was not published more than one year prior to the priority date of the above-identified application and because Applicants reduced the invention to practice before the cited Ellerby et al. reference was published, this reference is not prior art with respect to the claimed invention.

In view of the above remarks and the Declaration under 37 C.F.R. §1.131 submitted herewith, Applicants respectfully request that the Examiner remove the rejection of claims 10 and 15 under 35 U.S.C. § 103.

Regarding the § 103 rejection of claims 11, 12, 16 and 17

The rejection of claims 11, 12, 16 and 17 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of WO 99/46284 as applied to claims 9 and 14 above, and Ellerby et al. as applied to claims 10 and 15 above, further in view of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, and Javadpour et al., is respectfully traversed.

As argued above in regard to the independent claims, Applicants contend that generalized side effects on normal cells would not have been expected and that, therefore, one skilled in the art would not have been motivated to make the recited chimeric peptide in order to avoid generalized side effects as asserted by the Examiner. Furthermore, as discussed above, Ellerby et al. is not prior art against the claims of the subject application. In sum, Applicants maintain that the cited art does not teach or suggest chimeric peptides that include an antimicrobial peptide linked to a prostate-homing peptide and that there would have been no motivation to substitute chimeric peptides for the art-recognized use of antimicrobial peptides alone. In the absence of a credible motivation to combine the cited references to produce a chimeric peptide containing both an antimicrobial peptide and a prostate-homing peptide, the claimed invention is unobvious over the cited references. Accordingly, Applicants respectfully request reconsideration and removal of the rejection of claims 11, 12, 16 and 17 under 35 U.S.C. § 103.

Regarding new claims 23 to 27

New claims 23 to 27 are directed to methods of selectively inducing apoptosis in normal prostate tissue *in vivo* by administering to a subject a chimeric prostate-homing pro-apoptotic peptide that contains a prostate-homing peptide linked to an antimicrobial peptide, where the chimeric peptide exhibits selective toxicity to normal prostate tissue and where the antimicrobial peptide has low mammalian cell toxicity when not linked to the prostate-homing peptide.

Applicants submit that the new claims, which rely on use of a chimeric peptide containing an antimicrobial peptide linked to a prostate-homing peptide, are unobvious over the cited references for the reasons described above. Essentially, Ellerby et al. is not properly cited as prior art, and the remaining references, either alone or in combination, do not teach or suggest use of the recited chimeric peptide or motivate one to substitute the recited chimeric peptide for an antimicrobial peptide alone. Furthermore, the cited references do not teach or suggest a biochemical prostatectomy of normal prostate tissue using a chimeric peptide as in the invention of new claims 23 to 27. In sum, Applicants submit that new claims 23 to 27 are unobvious over the cited references and further submit that these new claims are in condition for allowance.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

June 2, 2003
Date

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